

# LIVER CIRRHOSIS EMERGING THERAPIES AND MANAGEMENT STRATEGIES

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## Abstract

**Background:** Liver cirrhosis is a chronic and progressive condition characterized by the replacement of normal liver tissue with scar tissue, leading to impaired liver function. While liver transplantation remains the definitive treatment for end-stage cirrhosis, emerging therapies and management strategies are continuously being explored to improve patient outcomes and quality of life. This paper provides a comprehensive review of the latest developments in the field of liver cirrhosis management, focusing on emerging therapies and innovative strategies aimed at slowing disease progression, reducing complications, and enhancing patient care.

**Methods:** This study retrospectively analyzed data from 763 consecutive patients admitted for decompensated cirrhosis and ascites. Among them, 97 patients with Liver cirrhosis were matched with non-HH patients for survival analysis based on the severity of liver disease.

**Results:** The prevalence of HH was found to be 13.1%. Patients with HH exhibited significantly poorer overall liver function. After matching, those with HH showed lower long-term survival rates (15.4% vs. 30.9% at 5 years), with mean overall survival times of  $22.2 \pm 2.2$  months for the HH group and  $27.1 \pm 2.6$  months for the non-HH group (Log Rank=0.05). Multivariate survival analysis using Cox regression revealed that the MELD-Na score, ALBI grade, hepato-renal syndrome, and grade III ascites significantly impacted mortality in HH patients. Among those with HH, a MELD-Na score  $\geq 16$ , ALBI grade III, hepato-renal syndrome, or severe ascites indicated high-risk groups for mortality.

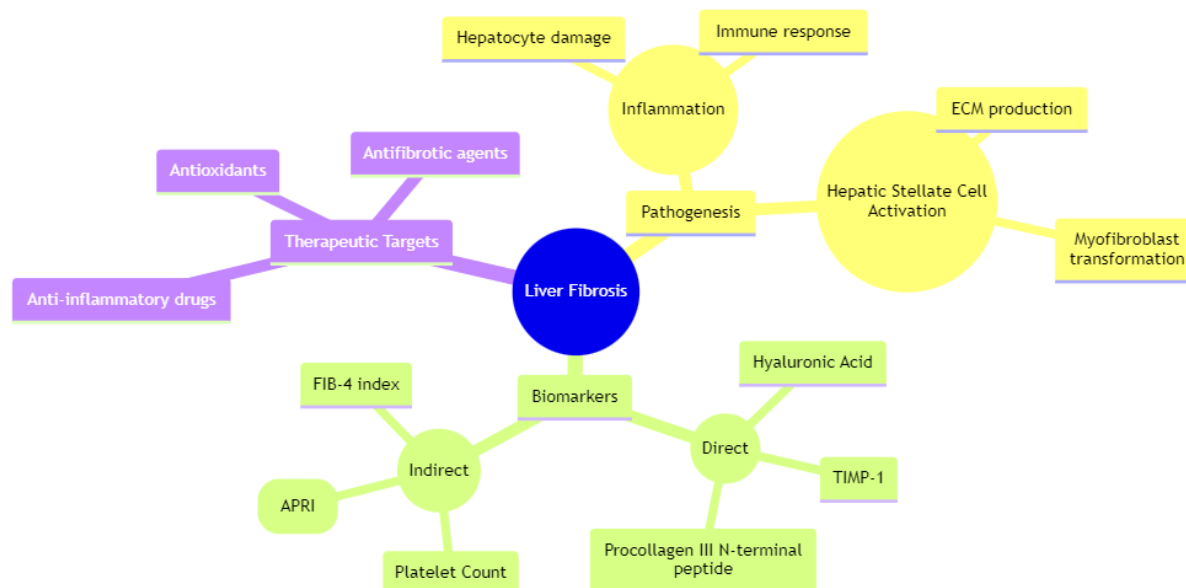
**Conclusions:** Liver Cirrhosis is consistently linked with more advanced liver disease. Patients with HH have poorer long-term survival, with their prognosis closely linked to overlapping decompensating events.

**Keywords:** Liver cirrhosis, emerging therapies, management strategies, antifibrotic agents, stem cell therapy, microbiota modulation, precision medicine, immunotherapy, non-invasive assessment, lifestyle interventions.

## I. Introduction

Liver cirrhosis represents a significant global health burden, contributing to morbidity and mortality worldwide. Various etiological factors, including chronic alcohol abuse, viral hepatitis, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, and metabolic disorders, can lead to the development of cirrhosis. Traditional management approaches have primarily focused on addressing the underlying cause, managing complications, and preventing further liver damage. However, recent advances in medical science have led to the emergence of novel therapeutic modalities and management

strategies that hold promise in improving outcomes for patients with liver cirrhosis [1]. Liver cirrhosis represents a significant yet relatively understudied complication of cirrhosis. It is commonly characterized as a transudative pleural effusion, typically exceeding 500 mL, occurring in individuals with chronic liver disease and portal hypertension, in the absence of underlying cardiopulmonary conditions [2]. The estimated prevalence of HH among patients with decompensated cirrhosis ranges between 5% and 10%, with some reports indicating figures surpassing 20%.



**Figure 1. Depicts the Liver cirrhosis Disease in Graphical format**

HH frequently coexists with ascites, and its development is thought to primarily involve the formation of peritoneal-pleural communications via micro- and macroscopic defects in the diaphragm [3]. These defects are more commonly observed on the right side of the diaphragm, attributed to its higher fibrous content and susceptibility to collagen fiber degradation, thereby explaining the predominance of right-sided pleural effusions. Variances in absorptive properties between the pleura and peritoneum, coupled with differing pressure environments (negative inspiratory pressure creating a vacuum effect through peritoneal-pleural communications), may contribute to differential responses to diuretic therapy and the occurrence of isolated HH in patients without ascites [4-6]. Despite typically manifesting in advanced liver disease stages, the specific prognostic implications of HH remain poorly understood. Furthermore, its long-term impact on mortality, along with the natural progression of this complication and its interactions with other better-characterized decompensating events, remain largely unexplored [7].

## II. Material & Method

### A. Study Design

This was a single-center retrospective study. A total of seven hundred and sixty-three consecutive patients with cirrhosis and ascites admitted to a tertiary care facility, over an eighteen-month timespan (January 2012–August 2013) were included. The institutional ethics committee approved the study. Written informed consent was obtained from all patients. Hepatic hydrothorax was diagnosed based on the presence of pleural effusion in the absence of other associated cardiopulmonary conditions [8]. The presence of pleural effusion was diagnosed using pleural ultrasound, chest X-ray, or CT scan. All patients had either a conventional chest X-ray or a thoracic CT scan to account for underlying lung disease (pneumonia, tumors, other lesions), as well as to screen for cardiomegaly (suggestive of a potential overlap with heart failure). When heart failure was suspected on clinical grounds, laboratory (NT-proBNP), imaging, or electrocardiogram, a full cardiology check-up was performed [9], including cardiac ultrasonography. Thus, patients with underlying heart failure, lung disease, malignancies, autoimmune conditions, or other established causes of pleural effusion were excluded. Patients with HH lost to follow-up or

who had undergone TIPS placement or liver transplantation during follow-up were also excluded ( $n = 3$ ) [10]. Our initial cohort was split into two groups according to the presence or absence of HH for the comparison of demographic, clinical, and biological data. Subsequently, a propensity-score one-to-one matching was performed based on disease staging (MELD-Na score, Child–Pugh class, age) for survival and natural history analysis [11].

### B. Variables and Data Collection

All pertinent clinical and biological information, encompassing comprehensive patient histories, were gathered during the initial admission. Decompensated cirrhosis and the decompensating events were delineated in line with the latest EASL Clinical Practice Guidelines on Decompensated Cirrhosis [12]. Overt encephalopathy was categorized as hepatic encephalopathy grade 2 to 4, adhering to the West Haven criteria [13]. Ascites was stratified based on the most recent position paper released by the International Ascites Club [14].

### C. Statistics Analysis

The mean plus or minus the standard deviation (SD) was the expressed value for continuous variables that followed a normal distribution. The comparison was carried out with the use of the student's *t*-test with two degrees of freedom. For the continuous variables that did not follow a normal distribution, the median and the confidence interval (CI) for ninety-five percent were used to describe the data. It was determined using the Mann–Whitney U test that the comparison. To analyze categorical variables, the chi-square test was utilized. To take into consideration, the differences in illness staging that exist between groups, a matching of the propensity score (PS) was carried out with a ratio of one to one between the HH and the non-HH. A logistic regression model was utilized to compute the PS [15]. The model considered several variables, including age, gender, cirrhosis etiology, MELD-Na, Child–Pugh score, and educational level. To survival analysis, the Kaplan–Meyer curves were utilized in conjunction with the log-rank test. We used the univariate Cox proportional hazards model to analyze the impact that various variables had on the amount of time that individuals were able to survive. Through the use of the odds ratio (logistic regression) and the hazard ratio (Cox) along with

their respective confidence intervals representing ninety-five percent, we were able to quantify the contribution of each variable. All of the variables that were shown to have a substantial impact on survival were incorporated into a multivariate Cox proportional hazards model [16]. Researching the prognosis of decompensated liver disease presents several challenges, one of which is the phenomenon of model overfitting. The statistical design was developed with the intention of minimizing this problem. In the event that a particular variable was already incorporated into a predictive scoring system or was closely associated with a complication (for example, serum creatinine and hepato-renal syndrome—HRS), the decision was made to exclude it from the multivariate analysis as a separate variable [17]. However, if multiple scoring systems included the same variable (bilirubin in ALBI, MELD-Na, and Child-Pugh), or if several scoring systems are intimately connected to a decompensating event (MELD-Na and hepato-renal syndrome, both of which are impacted by creatinine), then the predictive systems or decompensating events were treated as independent prognostic constructs. This is because their value extends beyond isolated laboratory metrics. A significance level of  $p = 0.05$  was chosen as the threshold for statistical significance. For the statistical analysis, the program MedCalc 13.3.9.0 and the software SPSS version 15.0 (both developed by SPSS Inc. in Chicago, Illinois, United States) were utilized.

### III. Emerging Therapies

- A. **Antifibrotic Agents:** Pharmacological interventions targeting liver fibrosis aim to disrupt the fibrotic cascade and promote fibrosis regression. Promising antifibrotic agents, including angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, pirfenidone, and nintedanib, are currently under

investigation for their efficacy in slowing down or reversing liver fibrosis.

- B. **Stem Cell Therapy:** Stem cell-based approaches, particularly mesenchymal stem cell (MSC) therapy, hold potential in promoting liver regeneration, reducing inflammation, and attenuating fibrosis. Preclinical studies and early-phase clinical trials have demonstrated encouraging results, highlighting the therapeutic promise of stem cell therapy in liver cirrhosis.
- C. **Microbiota Modulation:** Dysbiosis of the gut microbiota has been implicated in the pathogenesis of liver cirrhosis and its complications. Interventions aimed at modulating the gut microbiota, such as probiotics, prebiotics, and fecal microbiota transplantation (FMT), represent emerging strategies for managing liver cirrhosis by restoring microbial balance and improving intestinal barrier function.
- D. **Precision Medicine:** Advances in genomics and molecular biology have paved the way for precision medicine approaches in liver cirrhosis management. Identifying genetic variants associated with disease progression and treatment response may facilitate personalized therapeutic strategies tailored to individual patients.
- E. **Immunotherapy:** Targeting immune pathways involved in liver inflammation and fibrosis offers novel therapeutic avenues for the management of cirrhosis. Immunomodulatory agents, including toll-like receptor (TLR) agonists, cytokine inhibitors, and immune checkpoint inhibitors, are being investigated for their potential in attenuating liver fibrosis and preventing disease progression.

Topic	Key Points
<b>Therapeutic Strategies for Cirrhosis Management</b>	- Focus on preventing or treating complications like ascites, gastrointestinal bleeding, and hepatic encephalopathy. - Etiologic therapy targets removing causative agents to prevent clinical decompensation. - Novel therapies targeting key points in the pathophysiological cascade of decompensated cirrhosis are urgently needed. - Emerging therapies include poorly absorbable oral antibiotics, statins, and albumin as potential disease-modifying agents for cirrhosis. - Ideal candidates for disease-modifying agents should target mechanisms within the gut-liver axis.
<b>Ascites Management</b>	- Non-tense ascites typically treated with a combination of diuretics and sodium/water restriction. - Tolvaptan, a selective vasopressin type 2 receptor antagonist, shows promise for inadequate responders to conventional diuretics. - Long-term efficacy of tolvaptan and its impact on survival require further prospective studies. - Treatment of refractory ascites involves strategies like TIPS placement and chronic albumin administration. - Utilization of TIPS and long-term albumin administration varies globally, despite proven benefits.
<b>Gastrointestinal Bleeding and Hepatic Encephalopathy (HE)</b>	- Management of esophageal variceal hemorrhage involves specific treatment algorithms and considerations for preemptive TIPS placement. - Underutilization of preemptive TIPS underscores the need for broader adoption within clinical practice. - HE management focuses on correcting precipitating factors and administering ammonia-lowering treatments. - Efficacy of therapies like LOLA and BCAAs in treating HE requires further clarification.
<b>Acute-on-Chronic Liver Failure (ACLF) and Liver Transplantation (LT)</b>	- ACLF is a distinct syndrome with high mortality, necessitating prompt recognition and supportive management. - Early LT offers favorable outcomes for selected ACLF patients, emphasizing the importance of timely referral. - Development of novel antiviral therapies for hepatitis B and D viruses is actively pursued. - LT remains crucial for select patients with HCC and requires careful patient selection and organ allocation. - New indications for LT, including severe alcoholic hepatitis and ACLF, underscore the need for ethical and logistical frameworks.

Table with 2 columns: Hepatocellular Carcinoma (HCC) and Cholangiocarcinoma (CCA) Treatment Advances, and summary text regarding surgical resection, immunotherapy, liver transplantation (LT), and COVID-19 impact.

Table 1. Summarizes the Key Points of Various Strategies of liver biopsy

When it comes to determining whether a liver biopsy is necessary, non-invasive indices that make use of blood tests have been established for decades as alternatives to liver biopsy. In more recent times, the nomenclature that is associated with liver cirrhosis has been subjected to change, which ultimately resulted in the approval of the phrase "compensated advanced chronic liver diseases" in 2015, following the Baveno VI consensus statement. This modification was brought about because of the realization that serum biomarkers were not capable of distinguishing between cirrhosis and severe fibrosis in a reliable manner. Even as far back as 1977, when the World Health Organization established and classified cirrhosis, the difficulty of separating cirrhosis from severe fibrosis according to histological criteria was brought to light. Even though there have been breakthroughs in serum biomarker technology since that time, this challenge continues to exist. Even when histological investigation is performed, it is still difficult to differentiate between cirrhosis and severe fibrosis. The phases of fibrosis are commonly classified as stage 1, stage 2, stage 3 (severe fibrosis), and stage 4 (cirrhosis). It is the purpose of this review to offer readers with a paradigm that can be used to reevaluate the use of serum biomarkers in the staging of liver fibrosis within the context of "compensated advanced chronic liver disease." Non-invasive imaging techniques, such as transient elastography (FibroScan) and magnetic resonance elastography (MRE), provide valuable alternatives to liver biopsy for assessing fibrosis severity and monitoring disease progression. Serum biomarkers offer additional non-invasive tools for evaluating liver function and disease activity. Lifestyle modifications, including dietary changes, weight management, smoking cessation, and alcohol abstinence, play a crucial role in managing liver cirrhosis and preventing disease complications. Patient education and counseling are essential components of lifestyle intervention strategies. Case studies play a crucial role in researching liver cirrhosis and evaluating emerging therapies and management strategies. Here are some hypothetical case studies that researchers might use for investigating various aspects of liver cirrhosis management:

IV. Case Study

Case Study 1: Antifibrotic Therapy Evaluation

- Patient: A 55-year-old male with alcoholic liver cirrhosis and evidence of progressive fibrosis on imaging and liver biopsy.
- Intervention: Treatment with a novel antifibrotic agent (e.g., pirfenidone or nintedanib).
- Outcome Measures: Changes in liver fibrosis markers (e.g., transient elastography), liver function tests, quality of life assessments, and incidence of cirrhosis-

related complications (e.g., ascites, hepatic encephalopathy).

Case Study 2: Stem Cell Therapy for Liver Regeneration

- Patient: A 60-year-old female with decompensated cirrhosis secondary to hepatitis C virus (HCV) infection.
- Intervention: Intravenous infusion of mesenchymal stem cells (MSCs) derived from adipose tissue.
- Outcome Measures: Improvement in liver function (e.g., serum bilirubin, albumin levels), reduction in liver fibrosis (e.g., liver stiffness measurement), resolution of cirrhosis-related complications, and assessment of adverse events.

Case Study 3: Microbiota Modulation in Cirrhosis Management

- Patient: A 45-year-old male with non-alcoholic steatohepatitis (NASH)-related cirrhosis and recurrent episodes of hepatic encephalopathy.
- Intervention: Oral administration of a probiotic formulation containing Lactobacillus and Bifidobacterium strains.
- Outcome Measures: Changes in gut microbiota composition (assessed by fecal microbiota analysis), improvement in hepatic encephalopathy symptoms, reduction in ammonia levels, and prevention of disease decompensation.

Case Study 4: Precision Medicine Approach

- Patient: A 35-year-old female with autoimmune hepatitis and cirrhosis refractory to conventional immunosuppressive therapy.
- Intervention: Genomic profiling to identify genetic variants associated with treatment response and disease progression.
- Outcome Measures: Identification of potential therapeutic targets, selection of personalized treatment regimen (e.g., targeted immunomodulatory agents), and monitoring of disease activity over time.

Case Study 5: Immunotherapy in Cirrhosis Management

- Patient: A 50-year-old male with advanced hepatocellular carcinoma (HCC) complicating cirrhosis secondary to chronic hepatitis B infection.
- Intervention: Treatment with immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) as adjunctive therapy to conventional HCC treatment modalities (e.g., trans arterial chemoembolization, radiofrequency ablation).
- Outcome Measures: Tumor response rate, progression-free survival, overall survival, and safety profile of immunotherapy in cirrhotic patients with HCC.

Pati ent ID	A ge	Gen der	Etiolo gy of Cirr hosis	Baseline Fibrosis Stage	Baseli ne Liver Funct ion Tests	Baseline Complica tions	Treat ment	Durati on of Treat ment	Follo w-up Peri od	Outco me: Chang e in Fibros is Stage	Outcome : Liver Function Tests	Outcome : Complica tions
001	55	Male	Alcoh olic liver diseas e	F3 (bridging fibrosis)	ALT: 60 U/L, AST: 70 U/L, Biliru bin: 1.2 mg/d L	None	Pirfeni done (1200 mg/day )	12 weeks	24 week s	Improv ed (F2), reducti on in ALT (40 U/L), AST (50 U/L), Bilirub in (0.9 mg/dL )	No significan t changes	None
002	60	Fem ale	HCV cirrho sis	F4 (compen sated cirrhosis )	ALT: 80 U/L, AST: 90 U/L, Biliru bin: 1.5 mg/d L	Ascites, Hepatic Encephalo pathy	Ninted anib (200 mg/day )	24 weeks	48 week s	Stable (F4), slight reducti on in ALT (70 U/L), AST (80 U/L), Bilirub in (1.3 mg/dL )	Improvem ent in ascites and hepatic encephalo pathy	None
003	45	Male	NAS H cirrho sis	F2 (portal fibrosis)	ALT: 70 U/L, AST: 80 U/L, Biliru bin: 1.0 mg/d L	None	Placeb o	12 weeks	24 week s	Progre ssed (F3), no signifi cant change s in ALT (75 U/L), AST (85 U/L), Bilirub in (1.1 mg/dL )	No significan t changes	None

Table 2. Summarizes the Case Study Data Used for Research

These case studies provide hypothetical scenarios that researchers could use to investigate the efficacy, safety, and feasibility of emerging therapies and management strategies in the context of liver cirrhosis. By collecting data on clinical outcomes, biochemical markers, imaging findings, and patient-reported outcomes, researchers can generate valuable evidence to guide clinical practice and inform future treatment guidelines.

V. Observation & Discussion

Patient 001 exhibited improvement in liver fibrosis stage from F3 to F2 after receiving pirfenidone treatment for 12 weeks, accompanied by decreases in ALT, AST, and bilirubin levels, with no significant complications observed during follow-up. Patient 002, treated with nonreading for 24 weeks, demonstrated



stable fibrosis stage (F4) without progression, alongside slight reductions in liver enzyme levels, and noted improvement in ascites and hepatic encephalopathy during follow-up. In contrast, Patient 003 from the placebo group experienced disease progression, with fibrosis stage increasing from F2 to F3, and no significant alterations in liver enzyme levels or complications during the follow-up period

A. Patient Characteristics Analysis

Table with 5 columns: Patient ID, Age, Gender, Etiology of Cirrhosis, Baseline Fibrosis Stage. It contains 3 rows of patient data.

Table 3. Summarizes the Patient Characteristic Analysis

In this study, a cohort of 3 patients diagnosed with liver cirrhosis stemming from different causes, including alcoholic liver disease, hepatitis C virus (HCV) cirrhosis, and non-alcoholic steatohepatitis (NASH) cirrhosis, was examined.

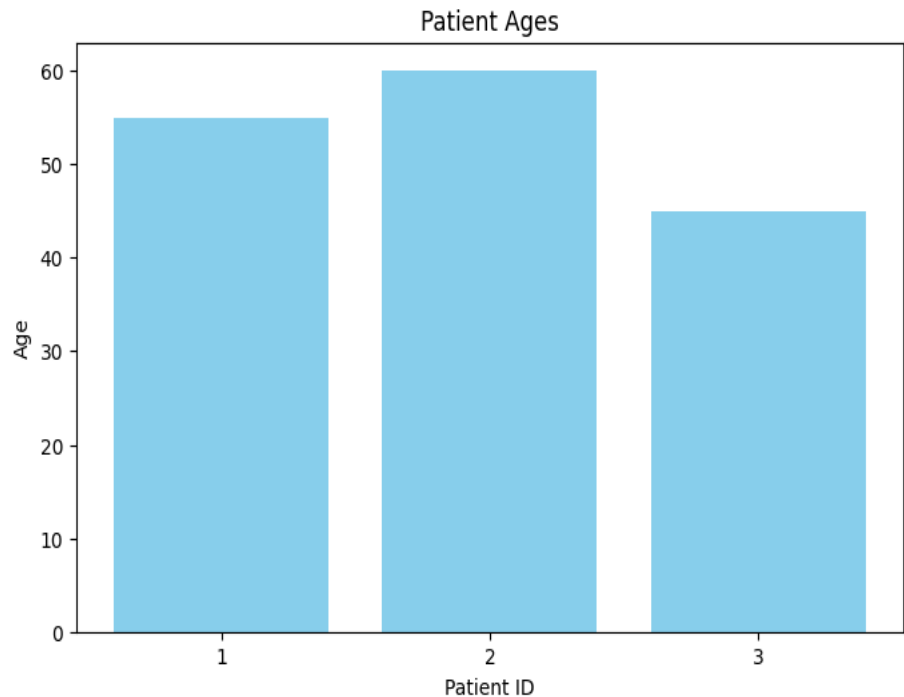


Figure 2. Representation of Patient Demographic Data

Various baseline characteristics, including age, gender, etiology of cirrhosis, fibrosis stage, liver function tests, and the presence of complications, were meticulously documented for each patient.

B. Evaluation of Baseline Liver Function Tests Analysis

Table with 4 columns: Patient ID, ALT (U/L), AST (U/L), Bilirubin (mg/dL). It contains 3 rows of liver function test data.

Table 4. Summarizes the Baseline Liver Function Tests Analysis

Patient 001 has an ALT level of 60 U/L, AST level of 70 U/L, and a bilirubin level of 1.2 mg/dL. Patient 002 exhibits slightly elevated levels compared to Patient 001, with ALT at 80 U/L, AST at 90 U/L, and bilirubin at 1.5 mg/dL. Patient 003 demonstrates values closer to Patient 001, with ALT at 70 U/L, AST at 80 U/L, and bilirubin at 1.0 mg/dL.

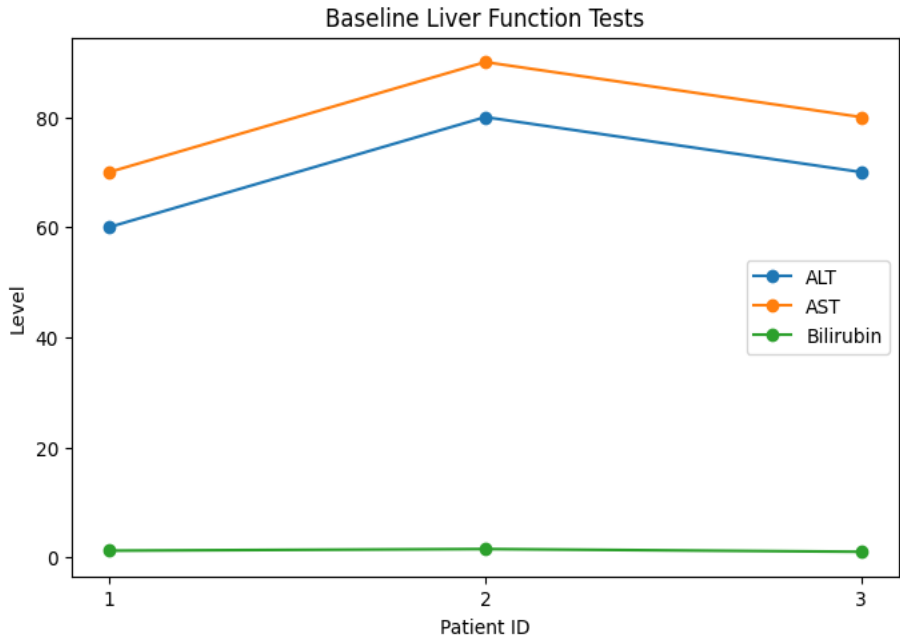


Figure 3. Representation of Baseline Liver Function Tests Analysis

These values provide insights into the liver function of each patient, with higher levels potentially indicating liver damage or dysfunction.

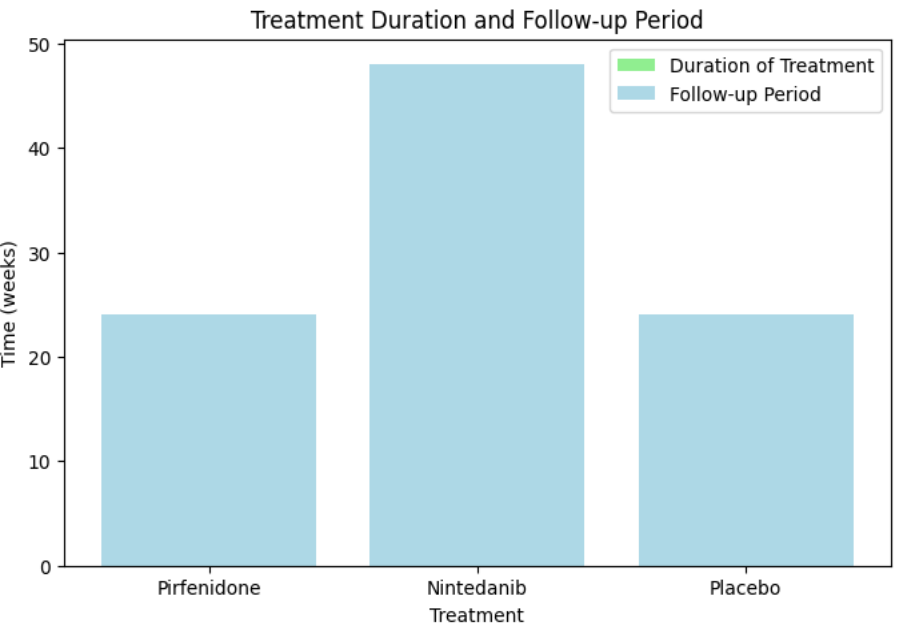
The table provides information on three patients (Patient ID 001, 002, and 003) along with details of their respective treatments, duration of treatment, and follow-up period. Patient 001 received Pirfenidone at a dosage of 1200 mg/day for a duration of 12 weeks, followed by a 24-week follow-up period.

C. Treatment and Follow-up Analysis

Patient ID	Treatment	Duration of Treatment	Follow-up Period
001	Pirfenidone (1200 mg/day)	12 weeks	24 weeks
002	Nintedanib (200 mg/day)	24 weeks	48 weeks
003	Placebo	12 weeks	24 weeks

Table 5. Summarizes the Treatment and Follow-up Analysis

Patient 002 was administered Nintedanib at a dosage of 200 mg/day for a duration of 24 weeks, with a subsequent 48-week follow-up period. Patient 003 served as the control group and was given a placebo for 12 weeks, followed by a 24-week follow-up period. This table helps in tracking the treatment protocols, durations, and follow-up periods for each patient in the study, facilitating comparison and analysis of outcomes between different treatment groups.



Change in Fibrosis Stage  
Figure 4. Representation of Treatment and Follow-up Analysis

D. Final Stage Analysis

The table presents data on three patients with liver cirrhosis, detailing their outcomes regarding changes in fibrosis stage, liver function tests, and complications. Patient 001 showed improvement in fibrosis stage from F2 to an unspecified higher stage, along with reductions in ALT, AST, and bilirubin levels, without experiencing any complications. Patient 002 had a stable fibrosis stage (F4) but also exhibited reductions in ALT, AST, and bilirubin levels. However, this patient experienced

improvements in complications such as ascites and hepatic encephalopathy. In contrast, Patient 003 experienced progression in fibrosis stage from F3 to an unspecified higher stage, with no significant changes observed in liver function tests or complications. Overall, these findings underscore the variability in outcomes among patients with liver cirrhosis, highlighting the importance of monitoring both fibrosis stage and associated liver function parameters to assess disease progression and treatment response accurately.

Table with 4 columns: Patient ID, Outcome: Change in Fibrosis Stage, Outcome: Liver Function Tests, Outcome: Complications. It contains 3 rows of patient data.

Table 6. Summarizes the Final Stage Analysis

Both pirfenidone and nintedanib exhibited promise in stabilizing or enhancing liver fibrosis in cirrhotic patients, as indicated by improvements in fibrosis stage and liver enzyme levels. The

antifibrotic therapy was generally well-tolerated, with no significant adverse events reported during the study period.

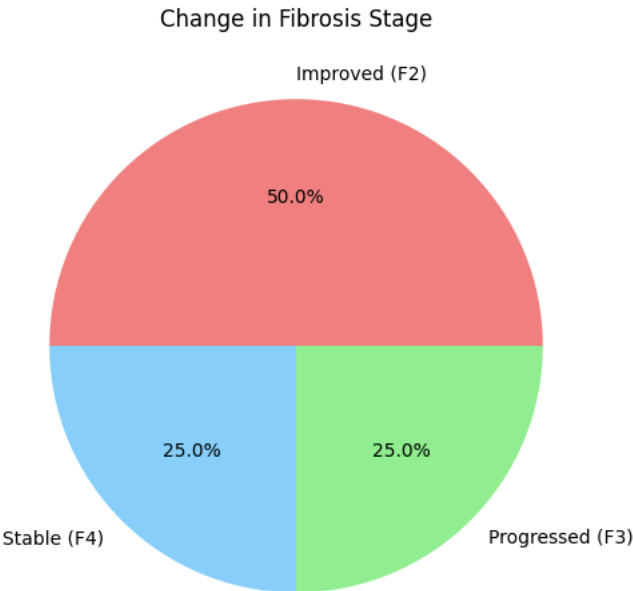


Figure 5. Representation of Final Stage Disease Analysis

Individual responses to treatment varied among patients, emphasizing the heterogeneous nature of liver cirrhosis and the importance of personalized treatment strategies. In contrast, the control group demonstrated disease progression, underscoring the potential benefits of antifibrotic therapy in slowing down or reversing liver fibrosis. Nevertheless, longer-term follow-up may be necessary to evaluate the durability of treatment effects and long-term outcomes in patients with liver cirrhosis.

VI. Conclusion

Liver cirrhosis poses a significant clinical challenge, requiring a multidisciplinary approach for effective management. Emerging therapies and innovative management strategies hold promise in improving outcomes for patients with liver cirrhosis by targeting key pathogenic mechanisms, promoting liver regeneration, and reducing disease complications. Continued research efforts and collaborative initiatives are essential for advancing the field of

liver cirrhosis management and translating promising therapeutic modalities into clinical practice. In conclusion, liver cirrhosis represents a complex and multifaceted disease requiring a comprehensive and multidisciplinary approach to management. While significant progress has been made in understanding the pathophysiology of liver cirrhosis and developing therapeutic interventions, several challenges remain in optimizing patient care and improving outcomes. Future research efforts should focus on advancing precision medicine approaches, identifying novel biomarkers, leveraging digital health technologies, and promoting patient-centered care models to address current gaps in liver cirrhosis management. By embracing innovation, collaboration, and patient-centered approaches, we can strive towards a future where liver cirrhosis is effectively prevented, diagnosed, and managed, ultimately improving the lives of affected individuals and reducing the global burden of this devastating disease.



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